

## PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:  
 United States Patent and Trademark  
 Office  
 (Box PCT)  
 Crystal Plaza 2  
 Washington, DC 20231  
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 May 1999 (18.05.99)	Priority date (day/month/year) 23 September 1997 (23.09.97)
International application No. PCT/EP98/05720	Applicant's or agent's file reference PCS9455JRH
International filing date (day/month/year) 04 September 1998 (04.09.98)	
Applicant HUATAN, Hiep	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

17 March 1999 (17.03.99)

in a notice effecting later election filed with the International Bureau on:

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  C. Cupello  Telephone No.: (41-22) 338.83.38
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**FOR THE PURPOSES OF INFORMATION ONLY**

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DK	Denmark	LR	Liberia	SG	Singapore		

## PARENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PCS9455JRH</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 98/ 05720</b>	International filing date (day/month/year) <b>04/09/1998</b>	(Earliest) Priority Date (day/month/year) <b>23/09/1997</b>
Applicant <b>PFIZER LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1.  Certain claims were found unsearchable (see Box I).
2.  Unity of invention is lacking (see Box II).
3.  The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
  - filed with the international application.
  - furnished by the applicant separately from the international application,
    - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - Transcribed by this Authority
4. With regard to the title,  the text is approved as submitted by the applicant
  the text has been established by this Authority to read as follows:
5. With regard to the abstract,
  - the text is approved as submitted by the applicant
  - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 

Figure No. \_\_\_\_\_

  - as suggested by the applicant.
  - because the applicant failed to suggest a figure.
  - because this figure better characterizes the invention.

None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/05720

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

**Remark:** Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 98/05720

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/35 A61K31/365 A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 311 195 A (MERCK) 12 April 1989 cited in the application see claims 1,7,15 ---	1-21
A	EP 0 240 274 A (MERCK) 7 October 1987 cited in the application see claims 1,7 ---	1-21
A	EP 0 473 223 A (MERCK) 4 March 1992 cited in the application see claims 1,3 see examples 7-12 ---	1-21
A	EP 0 537 998 A (MERCK) 21 April 1993 cited in the application see claims 1,7 see page 3, line 2 -----	1-21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search  26 January 1999	Date of mailing of the international search report  02/02/1999
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Scarpone, U

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

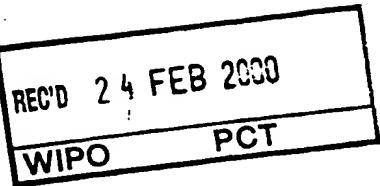
International Application No

PCT/EP 98/05720

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 311195	A	12-04-1989	US	4847243 A	11-07-1989
			AU	2355688 A	20-04-1989
			DE	3883338 A	23-09-1993
EP 240274	A	07-10-1987	AU	587895 B	31-08-1989
			AU	7100087 A	08-10-1987
			JP	62265223 A	18-11-1987
EP 473223	A	04-03-1992	AT	122230 T	15-05-1995
			AU	645594 B	20-01-1994
			AU	8267891 A	27-02-1992
			CA	2049668 A	23-02-1992
			DE	69109581 D	14-06-1995
			DE	69109581 T	18-01-1996
			DK	473223 T	10-07-1995
			ES	2072530 T	16-07-1995
			IE	67141 B	06-03-1996
			IL	99180 A	04-01-1998
			JP	2588328 B	05-03-1997
			JP	4230621 A	19-08-1992
			NZ	239370 A	27-04-1994
			PT	98708 A	31-08-1992
			US	5837228 A	17-11-1998
EP 537998	A	21-04-1993	US	5411737 A	02-05-1995
			AT	147621 T	15-02-1997
			AU	656815 B	16-02-1995
			AU	2701792 A	22-04-1993
			CA	2080574 A	16-04-1993
			DE	69216755 D	27-02-1997
			DE	69216755 T	24-07-1997
			FI	924640 A	16-04-1993
			JP	2649002 B	03-09-1997
			JP	5194187 A	03-08-1993
			ZA	9207908 A	14-07-1993

## PATENT COOPERATION TREATY

PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCS9455JRH	<b>FOR FURTHER ACTION</b> <small>See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)</small>	
International application No. PCT/EP98/05720	International filing date (day/month/year) 04/09/1998	Priority date (day/month/year) 23/09/1997
International Patent Classification (IPC) or national classification and IPC A61K31/35		
Applicant PFIZER LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 17/03/1999	Date of completion of this report 17.01.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Heller, D Telephone No. +49 89 2399 8746



INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

International application No. PCT/EP98/05720

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-10 as originally filed

**Claims, No.:**

1-16 as originally filed

17-24 as received on 03/11/1999 with letter of 26/10/1999

**Drawings, sheets:**

1/2,2/2 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:  
 the claims, Nos.:  
 the drawings, sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.  
 claims Nos. 17-19, 21.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP98/05720

because:

the said international application, or the said claims Nos. 17-19, 21 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 5-7, 9, 11, 15, 16, 22, 23
	No:	Claims 1-4, 8, 10, 12-14, 17-21, 24
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-24
Industrial applicability (IA)	Yes:	Claims see section III and V
	No:	Claims

**2. Citations and explanations**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/05720

**Section III:**

Claims 17 to 19 and 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Section V:**

**Prior art**

Reference is made to the following documents:

- D1: EP-A-0 311 195 (MERCK) 12 April 1989 cited in the application
- D2: EP-A-0 240 274 (MERCK) 7 October 1987 cited in the application
- D3: EP-A-0 473 223 (MERCK) 4 March 1992 cited in the application
- D4: EP-A-0 537 998 (MERCK) 21 April 1993 cited in the application

**Novelty**

The subject-matter of claims 1 to 4, 8, 10, 12 to 14, 17 to 21 and 24 is not new in the sense of Article 33 (2) PCT.

As far as claim 1 lacks further technical feature which would characterise an implantable tablet, its subject-matter discloses nothing more than a tablet (cf. examples of the present application). Every tablet comprises tableting excipients including a bulking agent.

Claim 1 is not novel, since the following documents disclose a tablet comprising a parasiticidal compound.

The process how to prepare such a tablet is not disclosed in D1 or D2, but it is also not claimed in present claim 1 and therefore irrelevant for novelty and inventive step.

D1 concerns the utility of avermectin compounds, in particular ivermectin, to prevent the effects of fescue toxicosis in animals grazing on tall fescue infected with fungi (page 2, lines 39 and 40). The active compound can be fed to the animal by incorporating it into the animal's feed or drinking water or it can be administered in a unit dosage form

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EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/05720

either orally as a drench, tablet, bolus or sustained release bolus or parenterally by injection or from a subcutaneous implant, or by a topically applied solution or suspension (page 6, lines 4 to 7; claims 1, 6, 7, 11, 13, 15).

Therefore, D1 anticipates novelty of present claims 1 to 4, 8, 12 and 18 to 21.

D2 discloses a similar subject matter as D1 (claims 1, 6, 7, 10). Therefore, present claims 1 to 4, 8, 12 and 18 to 21 are not new over D1.

D4 relates to a drug delivery device which is designed to provide for the release of the active drug over a prolonged period of time. In one embodiment of the device the drug that is delivered by the device provides protection for the wearer of the device against parasites. The preferred drugs are those of the avermectin and milbemycin families of drugs which are active antiparasitic agents against internal and external parasites (page 2, lines 30 to 37). The drug or active agent could be any substance administered topically in the form of a collar or transdermal patch; or any drug or substance administered by a suppository, rectal or vaginal; or any drug or substance administered by a subcutaneous implant; or any drug or substance administered orally by a tablet, capsule or ruminal bolus (page 2, last sentence bridging page 3).

As D4 contains calcium stearate (page 5, line 10), which is a tableting excipient, the following claims are not new over D4: claims 1 (page 3, line 2) to 4, 10 (page 5, line 8), 12, 13, 14 (page 5, line 21), 17 to 21, 24.

D3 is directed to a poly(ortho ester) implant synthesized by a condensation reaction of polyol monomers, including the polyol anthelmintic drug ivermectin, with a diketene acetal to form a potent implantable dosage form useful against various developmental stages of *Dirofilaria immitis*, a filarial parasite and causative organism of canine heartworm disease.

D3 discloses a ivermectin/poly(ortho ester) cross linked implant formed by a polymerisation reaction. The resulting paste further contains a stabilizer and an antioxidant (page 7, lines 15 to 23).

As D3 is silent to tableting excipients including a bulking agent, present claims 1 to 24 are new over D3.

The subject-matter of claims 5 to 7, 9, 11, 15 and 16, 22 and 23 is new in the sense of Article 33 (2) PCT.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/05720

**Inventive step**

The subject-matter of claims 5 to 7, 9, 11, 15 and 16, 22 and 23 does not involve an inventive step in the sense of Article 33 (3) PCT.

The additional features of claims 5 and 15 can be determined as alternatives and are therefore not inventive in the sense of Article 33 (3) PCT.

The same applies to claims 6, 7, and 9, which are directed to well-known tabletting excipients.

The features of claims 11 and 16 are also well-known from D3 (present claim 11: D3, page 7, line 20; present claim 16: D3, page 5, line 52). Therefore, the person skilled in the art can derive the teaching of claims 11 and 16 from D3.

According to Article 33 (3) PCT, claims 11 and 16 are not inventive.

The additional features of claims 22 and 23 can be determined by routine experiments and are therefore not inventive in the sense of Article 33 (3) PCT.

Even if the applicant is able to establish novelty no surprising aspect of the application as filed is described. Therefore, present claims 1 to 24 are not inventive according to the prior art as described above (Article 33 (3) PCT).

**Industrial applicability**

For the assessment of the present claims 17 to 19 and 21 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

17. Use of an antioxidant or a reducing agent in a formulation containing an avermectin or a milbemycin for preventing degradation of the avermectin or milbemycin.
18. The use as claimed in claim 17, wherein the formulation is suitable for sterilization, or has been sterilized, by irradiation.
- 5 19. The use as claimed in claim 17 or claim 18, wherein the formulation is not liquid.
20. A process for the production of an implant as defined in claim 1, which comprises mixing the parasiticidal compound with the tabletting excipients and forming into the desired shape.
- 10 21. A method for the treatment or prevention of parasitic infections which comprises administering an implant as defined in any one of claims 1-16 to an animal in need of such treatment.
22. An implant as claimed in claim 1, wherein greater than 95% by weight of the implant is made up of parasiticidal compound and tabletting excipients.
- 15 23. An implant as claimed in claim 22, wherein greater than 99% by weight of the implant is made up of parasiticidal compound and tabletting excipients.
24. A process for the production of an implant as defined in claim 12, which comprises mixing the parasiticidal compound with the tabletting excipients and an antioxidant or a reducing agent; forming into the desired shape; and sterilizing by irradiation.